CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-711

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 21-711, VASOVIST Injection Date: 19-DEC-2008

Introduction

VASOVIST (gadofosveset trisodium) 244 mg/mL (as the monohydrate) for intravenous injection is indicated for use in MRI angiography.

This solution formulation drug product is proposed to be packaged in 10 mL and 20 mL single-use bososilicate glass vials with bromobutyl rubber stoppers and aluminum seals. The recommended dose is 0.12 mL/Kg iv over 30 seconds followed by 25-30 mL normal saline flush.

The shelf life of the drug product is thirty six (36) months at controlled room temperature.

Adminstrative

The original submission of this 505(b)(1) NDA was received 12-DEC-2003 from EPIX Pharmaceuticals. On 26-AUG-2004, CMC found the application to be acceptable. However, the original NDA was not approved for clinical reasons. For this resubmission, there were no substantive CMC changes. The establishments were re-entered into EES and on 02-SEP-2008, and overall acceptable evaluation was provided.

There are no outstanding CMC deficiencies or agreements.

ONDQA recommends approval (AP).

Drug Substance (Gadofosveset trisodium)
$C_{33}H_{40}GdN_3Na_3O_{15}P$ and the molecular weight is 975.88 (957.86 on an anhydrous basis).

Gadofosveset trisodium is a trisodium salt of a gadolinium(III) complex of a substituted diethylenetriaminepentaacetate (DTPA) ligand. It is a white to slightly yellow powder which is hygroscopic and soluble in water. The retest period of the drug substance is 36 months.

[ ] b(4)

Gadofosveset trisodium contains two chiral centers and exists as an equilibrium mixture of two interconvertible diastereomers [ ] Chirality in gadofosveset trisodium is associated with the ligand metal interactions around the gadolinium atom.

Drug Product (VASOVIST)

VASOVIST is a sterile, preservative-free, clear, colorless to pale yellow, non pyrogenic solution of 244 mg of gadofosveset trisodium, 0.27 mg of fosveset, and water for injection in which the pH has been adjusted to 6.5 to 8.0. Fosveset is a ligand [ ] b(4)

Rik Lostritto, Ph.D., Director, ONDQA Division III

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Lostritto
12/19/2008 04:56:34 PM
CHEMIST

CMC REVIEW OF NDA 21-711

REVIEW # 1

Vasovist
Gadofosveset Trisodium Injection

Epix Laboratories

JOSEPHINE M. JEE
CMC REVIEWER

OFFICE OF NEW DRUG QUALITY ASSESSMENT
DIVISION OF PREMARKETING ASSESSMENT AND MANUFACTURING SCIENCE (BRANCH V)

FOR THE DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS (HFD-160)

Table of Contents

1. NDA 21-711
2. REVIEW: Resubmission No. 1
3. REVIEW DATE: 20-NOV-2008
4. REVIEWER: Josephine M. Jee
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Fludarabine phosphate	
Pre-NDA	None
Pre-NDA CMC Mtg	None
NDA 21-711, Original	12-DEC-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-711 Resubmission	30-JUN-2008
NDA 21-711 Amend.	08-JAN-2005
NDA 21-711 Amend(Mtg. Min.)	04-FEB-2005
NDA 21-711 Amend (Resp. to AE Letter.)	23-MAY-2005
NDA 21-711 Amend (Phase IV Study)	01-AUG-2005
NDA 21-711 Amend (Response to Request for information)	24-AUG-2005
NDA 21-711 Amend (Response to Request for Info.)	01-SEP-2005
NDA 21-711 Amend.(Response to Request for Info.)	10-OCT-2005
NDA 21-711 Amend (Election under 21 CFR § 314.110(a)	01-DEC-2005
NDA 21-711 Amend (Mtg. Req.)	05-DEC-2005
NDA 21-711 Amend (Mtg. Package)	21-DEC-2005
NDA 21-711 Amend (Revised Mtg. Package)	03-JAN-2006
NDA 21-711 Amend (Sponsor Mtg. Min)	12-JAN-2006
NDA 21-711 Amend (New Contacts)	27-JAN-2006
NDA 21-711 Amend (Mtg. Req.)	02-FEB-2006
NDA 21-711 Amend (Req. to Change Mtg. Min)	17-FEB-2006
NDA 21-711 Amend (Briefing Package)	03-MAR-2006
NDA 21-711 Amend (Requested List of Questions)	09-MAR-2006
NDA 21-711 Amend (Rev. List of Attendees)	29-MAR-2006
NDA 21-711 Amend (Mtg. Agenda)	03-APR-2006
NDA 21-711 Amend (Response to Information Request)	31-MAY-2006
NDA 21-711 Amend (Agreement to an Ext. of the Rev. Per.)	30-NOV-2006
NDA 21-711 Amend (Response to Request for info)	17-MAY-2007
NDA 21-711 Amend (Request for info)	21-MAY-2007
NDA 21-711 Amend (Type A Mtg Req)	30-AUG-2007
NDA 21-711 Amend (Resp. to Req. for info)	15-OCT-2007
NDA 21-711 Amend (Mtg. Min)	26-OCT-2007
NDA 21-711 Amend (Mtg. of teleconf)	07-NOV-2007
NDA 21-711 Amend (Revised Protocol)	14-NOV-2007
NDA 21-711 Amend (Revised Protocol)	21-DEC-2007
NDA 21-711 Amend (Protocol Correction)	23-JAN-2008
NDA 21-711 Amend (Req. for Teleconf)	03-APR-2008
NDA 21-711 Amend (Type C Mtg)	01-MAY-2008
NDA 21-711 Amendment (Vasovist –Confirmation of Tradename)	14-AUG-2008

7. NAME & ADDRESS OF APPLICANT:

Name: EPIX Pharmaceuticals, Inc.

Address: 4 Maguire Road
Lexington, MA 02421

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Vasovist®

b) Non-Proprietary Name (USAN): Gadofosveset trisodium

International Nonproprietary Name (INN): Gadolinate(3–),aqua[N-[2-[bis[carboxymethyl]amino]ethyl]-N-[(*R*)-2-[bis[carboxymethyl]amino]-3-hydroxypropyl] glycine, 4,4-diphenylcyclohexyl-hydrogen phosphato(6–)]-, Trisodium

c) Code Name/# (ONDC only): MS–32520–R (Epix), 3720 (Mallinckrodt)
Internal Codes:

d) CAS Registry Number: 211570-55-7
193901-90-5 (anhydrous form)

e) CAS Name: Gadolinate(3–), aqua[[(4*R*)-4-[bis[(carboxy-κO)methyl] amino-κN]-6,9-bis[(carboxy-κO)methyl]-1-[(4,4- diphenyl cyclohexyl) oxy]-1-hydroxy-2-oxa-6,9-diaza-1-phosphaundecan-11-oic acid-κN6,κN9,κO11]-1-oxidato(6–)]-, trisodium

e) Laboratory Codes: None provided.

f) Chemical Name (IUPAC): Trisodium-{(2-(R)-[(4,4-diphenylcyclohexyl)-phosphonooxy methyl]diethylenetriaminepenta acetato)(aquo) gadolinium(III)

Alternative names:

g) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: MRI Contrast Agent
Indicated for Use with Magnetic Resonance Angiography for [ ]
in Adults with Suspected or Known Vascular Disease.

b(4)

11. DOSAGE FORM: Sterile Solution for Injection

12. STRENGTH/POTENCY: 244 mg/mL (monohydrate basis)

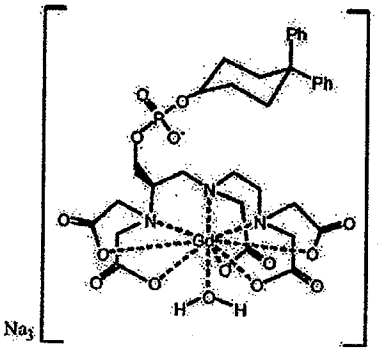
13. ROUTE OF ADMINISTRATION: IV

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product.

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Trisodium-{(2-(R)-[(4,4-diphenylcyclohexyl)-phosphonooxymethyl]diethylenetriaminepentaacetato)(aquo)gadolinium(III)



Molecular Formula: $C_{33}H_{40}GdNa_3O_{15}P$ **M.W.:** 975.88
957.86 (anhydrous form)

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
***							

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

*** **DMF** [ ] **DMF** [ ] b(4)
[ ] **and DMF** [ ] **were**
found acceptable by David Place, Ph.D's on 26-AUG-2004.

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	[ ]	Gadofosveset

b(4)

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A	N/A	Anthony Mucci	
EES	Site inspections	06-AUG-2008	S. Ferguson	Acceptable on 02-SEP-2008
Pharm/Tox	N/A	N/A		
Biopharm	N/A	N/A	Christy John	N/A
ODS/DMETS	N/A			
Methods Validation	N/A			
EA	N/A	N/A	J.Jee	Categorical exclusion granted (see attached review).
Microbiology	Consult		Dr. Brian Riley	Since there is no change in the sterilization process, it remains acceptable as the original evaluation.

The Chemistry Review for NDA 21-711

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC approved the original NDA on 26-AUG-2004. The resubmission review does not have significant changes. The changes proposed are in the synthesis steps to improve and decrease the levels of impurities in the drug substance and to improve the specifications of raw materials. From a Chemistry, Manufacturing and Controls standpoint, this New Drug Application is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 CMC commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

VASOVIST™ Injection is a clear, colorless to pale yellow, nonpyrogenic, sterile aqueous solution, containing 244 mg of gadofosveset trisodium (0.25 mmol), 0.27 mg of fosveset, and water for injection in which the pH has been adjusted to 6.5 to 8.0. No preservative is added to the solution. Fosveset is a ligand [ ]. VASOVIST™ (gadofosveset trisodium) Injection is a formulation of a stable gadolinium diethylenetriaminepentaacetic acid (GdDTPA) chelate substituted with a diphenylcyclohexylphosphate group, for use in magnetic resonance angiography (MRA). The drug product solution is tested for appearance, color at [ ] individual unspecified impurities, total unspecified impurities, total impurities, isomer ratio, viscosity, pH, sterility, endotoxin, osmolality, particle size, specific gravity, relaxivity, container closure integrity test, and volume. The proposed specifications are adequate. b(4) b(4)

VASOVIST™ Injection is packaged in clear, colorless, USP Type I borosilicate — glass vials (10 mL size and 20 mL size) sealed with bromobutyl rubber stoppers and aluminum flip-and-tear type seals. The drug product is terminally sterilized using moist heat. b(4)

The applicant provided long term (25°C /60% RH ± 5% RH, up **36 months**) and accelerated (40°C /75% RH, **6** months) stability data. The drug product has been shown to be stable under controlled room temperature conditions up to 36 months, and the **proposed 36 months expiry** is consistent with stability data submitted in the application.

VASOVIST™ Injection is the first MRI diagnostic contrast agent which has been optimized for vascular enhancement. The drug substance binds reversibly to human serum albumin and provides persistent signal enhancement of the vascular space throughout the body. VASOVIST™ Injection is to be administered by intravenous injection only.

The proposed expiration period for MS-325 Injection is 36 months, and the proposed label storage conditions: Store at 25°C (77°F); excursion permitted to 15-30°C (59-86°F); protect from light and protect from freezing. The drug product will be marketed in 10 mL fill in a 10 mL vial, 15 ml fill in a 20 mL vial.

An acceptable recommendation dated 02-SEP-2008 is received from the Office of Compliance for all facility sites.

Drug Substance:

[ ] b(4)

Gadofosveset trisodium contains two chiral centers and exists as an equilibrium mixture of two interconvertible diastereomers [ ] Chirality in Gadofosveset Trisodium is associated with the ligand metal interactions around the gadolinium atom. The relationship between the metal-based isomers may be either enantiomeric or diastereomeric, depending on the ligand structure. The drug substance is a 1.3 – 1.9: 1 mixture of Isomer A and Isomer B.

The molecular formula for gadofosveset trisodium is $C_{33}H_{40}GdN_3Na_3O_{15}P$ and the molecular weight is 975.88 (957.86 on an anhydrous basis).
Gadofosveset trisodium is a white to slightly yellow powder [ ] very soluble in water, hygropscopic in nature. The Differential Scanning Calorimetry shows gadofosveset trisodium decomposes at above 275°C. b(4)

The drug substance is tested for appearance, color : [ ] b(4)

], unspecified impurities (individual and total), total impurities, enantiomeric excess, isomer ratio, endotoxin, microbial content, water content.

Gadofosveset trisodium is accepted as a United States Adopted Name (USAN).

EPIX Labs. submitted batch analyses for thirteen (13) batches of gadofosveset trisodium drug substance. Up to 36 months of long-term (25°C /60%RH) stability data and 6 months of accelerated 40°C /75% RH stability data are submitted for 9 batches of gadofosveset trisodium drug substance. The drug substance has been shown to be stable in storage conditions tested for up to 36 months. The retest period proposed for Gadofosveset Trisodium is 36 months.

B. Description of How the Drug Product is Intended to be Used

VASOVIST Injection is a gadolinium-based blood pool contrast agent indicated for use with magnetic resonance angiography (MRA) to evaluate aortoiliac occlusive disease (AIOD) in adults with known or suspected peripheral vascular disease (1.1).

VASOVIST™ Injection should be administered as an intravenous bolus injection, manually or by power injection, at a dose of 0.12 mL/kg (0.03 mmol/kg) over a period of time up to 30 seconds followed by a 25-30 mL normal saline flush.

VASOVIST™ Injection is a clear, colorless to pale yellow solution containing 244 mg/mL (0.25 mmol/mL) of gadofosveset trisodium. VASOVIST™ Injection is supplied in 10 mL vials containing 10 mL of solution and 20 mL vials containing [ ]15 mL [ ] of solution. Each single dose vial is closed with a rubber stopper and an aluminum seal and the contents are sterile. Vials are contained in shipping cartons with the following configurations: (Item 4A.3) 10 mL single glass vials in individual cartons, boxes of 10 vials (NDC Code 50419-310-01) b(4)

20 mL single glass vials in individual cartons, boxes of 10 vials (NDC Code 50419-310-02)

VASOVIST™ Injection should be stored at 25°C (77°F: excursions permitted to 15-30°C (39-86°F) and protected from light and freezing.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is recommended for Approval from a Chemistry, Manufacturing, and Controls standpoint. The original NDA was recommended for approval on 26-AUG-2004. This resubmission contains no significant changes. The minor changes in the synthesis [b(4)] have improved the overall impurities levels. The final drug substance batch analysis showed lower levels in all the existing impurities.

The microbiology consult did not indicate any changes as compared to the original submission. Acceptable recommendation received from the Office of Compliance dated 02-SEP-2004for all facilities used in the manufacturing of drug substance and drug product.

III. Administrative

This NDA Resubmission was submitted electronically as a 505(b)(1) application. A Quality Overall Summary is included in the application.

A. Reviewer's Signature

See electronic signatures in Division File System (DFS).

B. Endorsement Block

See electronic signatures in DFS

C. CC Block

See DFS

66 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eldon Leutzinger
12/4/2008 09:49:25 AM
CHEMIST
For Josephine M. Jee.

Sarah Pope
12/4/2008 11:31:43 AM
CHEMIST
Concur

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21711/000
Org Code : 160
Priority : 1S

Sponsor: EPIX
71 ROGERS ST
CAMBRIDGE, MA 02142

Stamp Date : 15-DEC-2003
PDUFA Date : 01-JAN-2009
Action Goal :
District Goal: 02-NOV-2008

Brand Name : VASOVIST(GADOFOSVESET TRISODIUM)0.25MMO1
Estab. Name:
Generic Name: GADOFOSVESET TRISODIUM
Dosage Form: (INJECTION)
Strength : 0.25 MMOL/ML

FDA Contacts:			
	J. MOORE	Project Manager	301-796-2050
	J. JEE	Review Chemist	301-796-1375
	E. LEUTZINGER	Team Leader	301-796-1399

Overall Recommendation: ACCEPTABLE on 02-SEP-2008by S. FERGUSON(HFD-322) 301-796-3247
ACCEPTABLE on 26-AUG-2004by S. FERGUSON(HFD-322) 301-796-3247
ACCEPTABLE on 16-AUG-2004by DAMBROGIOJ
ACCEPTABLE on 26-JUL-2004by S. FERGUSON(HFD-322) 301-796-3247

---

b(4)

Establishment : CFN : [ ] FEI : [ ]
[ ]
[ ] b(4)
[ ]

DMF No: AADA:

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

HAZELWOOD, MO 63042

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-AUG-08

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : 1028892 FEI : 1028892

MALLINCKRODT MEDICAL INC

8800 DURANT RD

RALEIGH, NC 276163104

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : SVT OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-SEP-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [ ] FEI : [ ]

[ ] [ ] b(4)

[ ] b(4)

[ ]

DMF No: AADA:

Responsibilities: [ ] b(4)

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 08-AUG-08

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : [ ] FEI : [ ] b(4)

[ ]

[ ] b(4)

[ ]

DMF No: AADA:

Responsibilities: [ ] b(4)

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile :	CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	07-AUG-08		
Decision :	ACCEPTABLE		
Reason :	BASED ON PROFILE		

Appears This Way
On Original

NDA 21-711

VASOVIST (gadofoveset trisodium) Injection, 244 mg/mL

CHEMISTRY DIVISION DIRECTOR REVIEW #1

Applicant:

Epix Laboratories, Inc.
71 Rogers St.
Cambridge, MA

Indication: Imaging agent for Magnetic Resonance Angiography

Presentation: 10 and 20 mL vials containing 10, 15 — mL b(4)

EER Status: Acceptable 20-JUL-2004

Consults: DMETS – Tradename: Vasovist – not acceptable 1-MAR-2004
Statistics – None
EA – no consult - waiver requested – granted
Micro – acceptable 3-JUN-2004

Post Approval Agreements or Commitments: None

The original NDA was received 12-DEC-2003

The **drug substance** is manufactured by:

Tyco Healthcare/Mallinckrodt, Inc.
St. Louis, MO

Manufacturing and controls information was reviewed and were found acceptable. Note that the final drug substance (Gd ligand complex) is formed in situ and the finished drug product is directly manufactured.

Structural characterization of the drug substance was satisfactory. Chirality is introduced via an [ ] Specifications were found acceptable (after manufacture of — batches the specifications will be revisited and possibly updated, therefore these specifications are considered interim). Impurities specifications are adequate and are qualified from a safety perspective. b(4)

Conclusion
Drug substance is satisfactory.

The **drug product**: 10, 15, [ ] mL in 10 and 20 mL stoppered vials. b(4)

Manufacturer:

Tyco Healthcare/Mallinckrodt, Inc.
Raleigh, NC

[

] The manufacturing process is a standard formulation and vial filling operation with terminal moist heat sterilization. Adequate in-process controls are in place. The proposed regulatory specifications are acceptable, (after manufacture of— batches the specifications will be revisited and possibly updated), therefore these specifications are considered to be interim) The submitted stability data are adequate to support the requested 36 month expiry in all presentations. The stability testing protocol is considered adequate. The established name gadofosveset trisodium is USAN. b(4)

Labeling was not comprehensively reviewed. It is noted that there is an error on thwe immediate container and carton labels. Fosvaset content is stated to be [ ] however the correct content is 0.27 mg/mL. b(4)

The overall Compliance recommendation is acceptable as of 3-JUN-2004.

All associated DMFs are acceptable
Conclusion
Drug product is acceptable

Overall Conclusion
From a CMC perspective the application is recommended for approval pending labeling revision.

Eric P Duffy, PhD
Director, DNDC II/ONDC

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Duffy
1/7/05 04:38:49 PM
CHEMIST

Review of Chemistry, Manufacturing, and Controls

NDA No. 21–711

Vasovist

Gadofosveset Trisodium Injection

Epix Laboratories

by

Chemistry Reviewer: David A. Place, PhD

Division of New Drug Chemistry II – HFD-820

for

Clinical Review Division: HFD–160

Division of Medical Imaging and Radiopharmaceutical Drug Products

Table of Contents

Chemistry Review Data Sheet

1. **NDA** 21–711

2. **REVIEW #** 1

3. **REVIEW DATE:** 26–AUGUST–2004

4. **REVIEWER:** David A. Place, PhD, HFD-820

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
N/A	

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original	**12–DEC–2003**
Labeling Amendment	**10–FEB–2004**
Amendment	**20–AUG–2004**

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Epix Laboratories, Inc.
Address:	71 Rogers St., Cambridge, MA 02142
Representative:	Robert A. Morgan
Telephone:	**(617) 250–6000**

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: Vasovist®
b) Non-Proprietary Name: gadofosveset
c) **Code Name/# (ONDC only): MS–32520–R (Epix), 3720 (Mallinckrodt)**
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: S

9. **LEGAL BASIS FOR SUBMISSION:** N/A

10. **PHARMACOLOLGICAL CATEGORY/INDICATION:** MRI Contrast Agent

11. **DOSAGE FORM:** Sterile solution for injection

12. **STRENGTH/POTENCY:** 244 mg/mL (monohydrate basis)

13. **ROUTE OF ADMINISTRATION:** IV

14. • **OTC DISPENSED:** __X__ • • __OTC

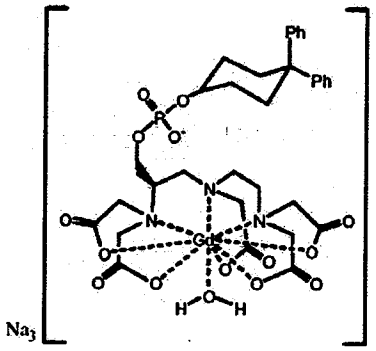
15. SPOTS (Special Products On-Line Tracking System)

___ SPOTS product – form Completed _X_ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): Trisodium-{(2-(R)-[(4,4-diphenylcyclohexyl)-phosphono-oxymethyl]diethylenetriaminepentaacetato)(aquo)gadolinium(III)

Structure:



Molecular formula: $C_{33}H_{40}GdNa_3O_{15}P$
Molecular Weight: 975.88 957.86 (anhydrous form)
CAS Registry No. 211570-55-7 193901-90-5 (anhydrous form)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODEa	STATUS b	DATE REVIEW COMPLETED	COMMENTS
[redacted]	3	[redacted]	[redacted]	3	Adequate	3/23/04	Guo
	3			3	Adequate	9/15/03	Lewis
	5			3	Adequate	2/4/04	Stevens-Riley

b(4)

a. Action codes for DMF Table:
1 – DMF Reviewed

Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

b Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	[redacted]	[redacted]

b(4)

US Patent (Expires): 5919967

Exclusivity: Five years requested.

18. STATUS:

ONDC:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending		Anthony Mucci
EES	Acceptable (all sites)	7/20/04	OC
Pharm/Tox	Pending		Siham Biade
Biopharm	Pending		Christy John
LNC	USAN Approved	N/A	
Methods Validation	To be requested after approval		
DMETS	Not Acceptable	3/1/04	Linda Wisniewski
EA	Categorical Exclusion Satisfactory	8/26/04	David Place
Microbiology	Acceptable	6/3/04	Brian Riley

OGD:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	N/A		
Methods Validation	N/A		
Labeling	N/A		
Bioequivalence	N/A		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only): ***Not Applicable***

The application submission(s) covered by this review was taken in the date order of receipt. _ Yes _ No
If no, explain reason(s) below:

Appears This Way
On Original

Chemistry Review for NDA 21–711

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
The chemistry recommendation is "Approval".

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
The sponsor should commit to those items identified in the Action Letter to Applicant. These fall under three broad categories.
1. Continued full characterization of the Drug Substance isomers (A & B)
2. Minimize GdEDTA in the drug substance and drug product
3. Provide confidence bands for the stability data plots for drug product.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is a novel derivative of the first approved MRI contrast agent, Gadolinium DTPA (Magnevist). A diphenylcyclohexyl moiety is attached to the backbone of the DTPA ligand by a phosphodiester linkage. The lipophilic group causes the drug substance to bind reversibly to **serum albumin. The clinical consequences are two–fold. First, the binding slows down the renal** elimination of the drug, enabling diagnostic imaging of the vasculature over a period up to an hour **post–injection. The currently approved gadolinium drugs are eliminated in minutes. Second, the** binding to the large albumin molecule slows down the tumbling rate of the gadolinium chelate, and increases its relaxation efficiency by an order of magnitude, reducing the molar dose required to a tenth of the currently approved gadolinium agents.

The drug substance has been shown to be stable in storage over a period of three years. The proposed regulatory specifications are adequate to control the purity of the drug substance.

The drug product is a 0.25 millimoles/mL sterile aqueous solution of drug substance with a trace of free ligand [ ] The long elimination time allows efficient **imaging of the vasculature through Magnetic Resonance Angiography (MRA). The currently–approved angiographic methodology calls for the intra–a**rterial injection of iodinated contrast media and CT scanning. The new drug has the advantage of greatly reducing anaphylactic reactions, as can occur with iodinated agents, and the injection route is the less invasive intravenous vs. intra-arterial administration. Another advantage is that MRI uses low energy radiofrequencies rather **than the potentially damaging x–rays used in conventional radiography.** b(4)

The drug product has been shown to be stable under controlled room temperature conditions up to three years, and the proposed 36 months expiry is consistent with stability data submitted in the application. The proposed regulatory specifications are adequate. The specifications will be reviewed after 30 production lots have been manufactured.

B. Description of How the Drug Product is Intended to be Used
As for all gadolinium–based MRI contrast media, Vasovist is intended for IV administration. This is an improvement over the current intra–arterial injection of iodinated contrast media.

C. Basis for Approvability or Not-Approval Recommendation
The application is recommended for approval based on the CMC data submitted.

III. – Administrative

A. – Reviewer's Signature

Chemist David A. Place, PhD _____ Date: 26-AUG-2004

B. – Endorsement Block Same date as draft review

Chemistry Team Leader Eldon Leutzinger, PhD _____ Date:

Project Manager _____ Date:

cc: Orig. NDA 21–711
HFD–160/Division File
HFD–820/ChemDivDir/EDuffy
HFD–160/DivDir/

57 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Place
8/26/04 01:23:17 PM
CHEMIST
Approval recommended with Phase 4 commitments

Eldon Leutzinger
8/26/04 02:47:32 PM
CHEMIST
I concur with the conclusions and the recommendation.